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Telbivudine Improves Renal Function in Patients With Chronic Hepatitis B

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BACKGROUND & AIMS: There is a close relationship between chronic hepatitis B virus infection and chronic renal disease. We analyzed changes in renal function using different markers of glomerular filtration rate (GFR) in multiple studies of telbivudine treatment of patients with chronic hepatitis B virus infection. **METHODS:** We used serum creatinine-based equations (ie, Cockcroft-Gault, Modification of Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration) to estimate GFR (eGFR) in adults with chronic hepatitis B virus infection and compensated liver disease who participated in a phase III, randomized, double-blind study comparing the efficacy and safety of telbivudine (600 mg/d) and lamivudine (100 mg/d) for 2 years (the GLOBE study) and in long-term extension studies (4−6 years), as well as in patients with decompensated cirrhosis (2 years). **RESULTS:** eGFRs calculated using the Cockcroft-Gault, Modification of Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration equations were concordant, indicating improved renal function in telbivudine-treated patients during the 2-year GLOBE study (there was an 8.5% increase in mean eGFR, based on the Modification of Diet in Renal Disease equation). Improved renal function was maintained for 4−6 years. Increased eGFR with telbivudine treatment was also observed in patients at increased risk for renal impairment: patients with baseline eGFRs of 60−89 mL/min/1.73 m^2 (+17.2%), older than 50 years (+11.4%), and with liver fibrosis/cirrhosis (+7.2% for patients with Ishak fibrosis score at 5−6). In decompensated patients with high renal risk, eGFR was also improved on telbivudine (+2.0%). **CONCLUSIONS:** In global trials of patients with compensated and decompensated cirrhosis, long-term telbivudine therapy was associated with a sustained improvement of renal function—particularly among patients with increased risk of renal impairment. The mechanisms of this renal protective effect remain to be determined.

Keywords: Telbivudine; Chronic Hepatitis B; Chronic Renal Disease; Glomerular Filtration Rate.

A close relationship exists between chronic hepatitis B (CHB) and chronic renal disease.[1] Chronic hepatitis B virus (HBV) infection can cause renal dysfunction through immune complex−mediated glomerular diseases, such as membranous nephropathy and mesangiocapillary glomerulonephritis.[2,3] In countries with endemic HBV infection, such as many within the Asia-Pacific region, HBV-related glomerulopathies are an important cause of end-stage renal disease and renal replacement therapy.[4]

Renal function, assessed by the estimated glomerular filtration rate (eGFR), is frequently impaired in patients with compensated CHB. The European Virgil database in 24 European centers showed that 15% and 4% of 381 CHB patients had eGFR at 50−80 mL/min or <50 mL/min before start of current therapy, respectively.[5] In a real-life cohort study including HBV-infected patients from 2 German centers, 20 of 60 patients had chronic kidney disease (CKD) stage 2 (eGFR at 60−89 mL/min) before starting antiviral treatment.[6] In a cohort study performed in 290 CHB Asian patients living in the United States, 35%−45% had CKD stage 2 at baseline.[7]

Renal dysfunction can also develop in patients with CHB with advanced/end-stage liver disease or decompensated cirrhosis through multiple mechanisms, including functional renal insufficiency (hepatorenal syndrome). In patients with

Abbreviations used in this paper: **CHB, chronic hepatitis B; CK, creatine kinase; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; IF, Ishak fibrosis score; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine.**

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decompensated CHB, creatinine clearance <70 mL/min was observed in 33% of patients with end-stage liver disease and renal function impairment was shown to be correlated with impaired liver function and mortality rates.[8–11]

Five oral antiviral treatments for CHB are currently available; 2 are nucleotides (adefovir and tenofovir) and 3 are nucleosides (lamivudine, entecavir, and telbivudine). These oral antiviral agents are all primarily eliminated unchanged through renal route.[12] Therefore, in patients with renal insufficiency, dose reduction and/or increased dose intervals are recommended. Renal impairment is frequent after long-term treatment with adefovir.[13,14] Similarly, a decrease of eGFR has been observed in retrospective cohorts of CHB patients during long-term tenofovir or entecavir-treated.[15–17] In a cohort of 737 tenofovir-treated CHB patients, serum creatinine (SCr) increased by ≥26 μmol/L in 3% of patients after a median of 16 months of therapy and dose reduction was required in 6% of patients due to worsened creatinine clearance.[15] In a longitudinal study of almost 200 CHB patients, either off treatment or treated with lamivudine, adefovir, entecavir, or tenofovir for 24 months, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR at baseline and end of follow-up using a linear mixed-effects models to predict time-related changes in renal function. Individual eGFR declined by approximately −2 mL/min/y in untreated patients and −1 mL/min/y in each of the treatment groups.[6] In another longitudinal study, >220 patients were treated with a nucleoside (lamivudine or entecavir), a nucleotide (adefovir or tenofovir), or combination nucleoside/nucleotide therapy for mean follow-up of 55 months. An increase in SCr ≥5% was observed in 32% of patients receiving a nucleoside, 52% receiving a nucleotide, and 16% receiving combination therapy.[18]

The aim of this review is to present overall analysis of renal function in telbivudine clinical trial database, focusing on the 2-year data from the GLOBE study and the subsequent long-term extension studies in patients with compensated CHB.[19] Populations of special interest were those patients most vulnerable for renal dysfunction, including the elderly and those with baseline renal insufficiency, severe liver fibrosis, or decompensated liver disease.

Methods

Patients From Telbivudine Clinical Trial Database Analyzed for Renal Function

GLOBE study. The GLOBE study (CLDT600A2302) was a randomized, double-blind, 104-week, phase III trial designed to compare the efficacy and safety of telbivudine (600 mg/d) and lamivudine (100 mg/d) in adults with CHB and compensated liver disease.[19] Patients with SCr >133 μmol/L at screening were excluded. In the intent-to-treat population (n = 1367; 921 hepatitis B e antigen [HBeAg]-positive and 446 HBeAg-negative), patients were randomized 1:1 to receive either telbivudine 600 mg daily for up to 104 weeks or lamivudine 100 mg daily for up to 104 weeks. HBeAg-positive patients were younger (32 years in the telbivudine group and 33 years in the lamivudine group) compared with HBeAg-negative patients (43 years in both treatment groups). At baseline, 37.6% (256 of 680) of patients in the telbivudine group and 34.1% (234 of 687) in the lamivudine group had CKD stage 2 (eGFR at 60−89 mL/min/1.73 m^2; Modification of Diet in Renal Disease [MDRD]). In the telbivudine and lamivudine groups, 65.3% and 64.3% of patients were of Asian origin, respectively.

Long-term extension studies of GLOBE. The study A2301 (CLDT600A2303) was an extension study for CHB patients who had successfully completed either the GLOBE study (CLDT600A2302) or Study 015 (NV-02B-015), both of which were similar in design to the GLOBE trial, but were conducted entirely in China. In the A2303 study, 82.6% of patients were of Asian origin. In this extension study, patients received an additional 2 years of open-label telbivudine treatment.[20–22] Patients who completed 2-year treatment with telbivudine or lamivudine in the GLOBE or 015 studies and who did not develop genotypic resistance to lamivudine or telbivudine and had undetectable serum HBV DNA at the end of the 2 years were enrolled in Study A2303, where they received open-labeled telbivudine treatment for an additional 2 years. At the end of Study A2303, patients were able to continue telbivudine treatment for an additional 2 years in extension studies CN04 and CN04E1. Of those patients who received 4−6 years of telbivudine treatment during these 4 studies (ie, GLOBE/015, A2303, CN04, and CN04+1), a total of 70 had evaluable paired liver biopsies at baseline and year 5.

Patients who switched from lamivudine in GLOBE study to telbivudine in study A2303. Of the 852 patients treated with lamivudine in the GLOBE and 015 studies, 398 without genotypic resistance at the end of the feeder studies rolled over to extension study 2303 to receive telbivudine for 2 additional years. Of these, 299 (171 HBeAg-positive and 128 HBeAg-negative) had undetectable HBV DNA at the time of switch. The effect of telbivudine switch on renal function was analyzed in this subgroup of patients.

Patients off treatment in the study A2303. At the end of the GLOBE and 015 studies, 66 patients met the per-protocol criteria for discontinuation of telbivudine treatment due to efficacy. Before treatment discontinuation, 98% of patients had undetectable HBV DNA (<300 copies/mL) and all had HBeAg seroconversion. Maintenance of eGFR improvement in patients off treatment was studied in these patients.

Decompensated CHB patients of the A2301 study. The study A2303 (CLDT600A2301) was a double-blind randomized controlled trial that compared telbivudine vs lamivudine in adult patients with decompensated CHB and evidence of cirrhosis.[23] In telbivudine and lamivudine groups, 64.9% of patients were of Asian origin. Patients were randomized 1:1 to 104-week treatment with telbivudine 600 mg/d or lamivudine 100 mg/d (n = 114 in each treatment group of the intent-to-treat population).

Assessment of Renal Function

The GFR was estimated by the following formulas based on SCr.

1. Cockcroft-Gault calculation for eGFR (mL/min) = $\frac{(140-\text{Age}\times\text{Weight})}{72\times\text{SCr}}\times$ 0.85 if female (with weight in kg and SCr in mg/dL).[24]

2. MDRD calculation for eGFR (mL/min/1.73 m^2) = 186 × creatinine (mg/dL)$^{-1.154}$ × age$^{-0.203}$ × 1.210 (if black) × 0.742 (if female).[25]

3. CKD-EPI calculation for eGFR (mL/min) = GFR = 141 × min(SCr/κ, 1)$^{\alpha}$ × max(SCr/κ, 1)$^{-1.209}$ × 0.993$^{\text{Age}}$ × 1.018

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(if female) × 1.159 (if black) where SCr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.[26]

Statistical Analysis

For the GLOBE and 2301 studies, where an active comparator was present, analysis of covariance model was used to test if there was any significant difference in eGFR between the 2 treatment groups (telbivudine vs lamivudine). The analysis of covariance model included treatment, country, and baseline values as covariates; means were calculated using the least square method. The last observation carried forward method was used. For the other studies, where all patients were on telbivudine, change from baseline within treatment group was analyzed using Student t test.

The baseline eGFR was classified into 3 categories: <60 mL/min/1.73 m^2, 60−89 mL/min/1.73 m^2 (CKD stage 2), and ≥90 mL/min/1.73 m^2 and a shift table allowed comparing changes of categories from baseline to end of study.

An exploratory analysis was performed to evidence the possible relationship between individual eGFR data from GLOBE Study and laboratory parameters (eg, alanine aminotransferase, total bilirubin, creatine kinase [CK]) or physiological parameters (eg, blood pressure, heart rate).

A multivariate analysis was performed to assess the factors predictive of shifting in eGFR (MDRD) to ≥90 mL/min/1.73 m^2 at year 2 in GLOBE study in patients with eGFR at 60−89 mL/min/1.73 m^2 at baseline. Stepwise regression methods were applied to select the variables in the logistic regression model ($P \leq .1$ to enter, $P \leq .1$ to stay).

Results

eGFR Changes in CHB Patients From the GLOBE Study (2 Years)

In the intent-to-treat population of the GLOBE study, 680 patients were randomized in the telbivudine treatment group and 687 patients in the lamivudine treatment group.[19] The mean overall treatment exposure was 100.2 weeks in the telbivudine treatment group and 99.3 weeks in the lamivudine treatment group.

Results in Table 1 indicate that all markers of renal function (SCr and 3 SCr-based estimating equations for GFR) were improved at weeks 52 and 104 for patients in telbivudine group compared with the lamivudine group. Figure 1 shows that renal function declined over time in lamivudine-treated patients, and renal function steadily improved in telbivudine-treated patients, with the greatest improvement seen during the second year of treatment. Results with CKD-EPI and MDRD equations were comparable during the 2 years of treatment (Figure 1).

Maintenance of eGFR Improvement in Long-Term Studies in CHB

The extension studies of GLOBE showed that the eGFR improvement was maintained during long-term telbivudine therapy. Thus, in the 2-year GLOBE extension, eGFR increased from baseline and remained significantly elevated during the 4 years of the study. The mean increase in eGFR was +14.9 mL/min/1.73 m^2 at week 208 ($P < .0001$) (Table 2). In 74% (165 of 223) of the telbivudine-treated patients with baseline eGFR of 60−89 mL/min/1.73 m^2 (CKD stage 2), renal function improved to ≥90 mL/min/1.73 m^2 after 4 years of treatment.

Long-term effect of telbivudine on eGFR was evaluated in patients who received overall 4 to 6 years of telbivudine treatment (extension study CN04E1). In this small study population, the absolute change in eGFR from baseline was statistically significant with +29.3 and +30.2 mL/min/1.73 m^2 at weeks 104 and 208, respectively (n = 70) (mean, MDRD). In 37 of 39 (94.9%) of patients with baseline CKD stage 2, renal function improved to normal at week 312; meanwhile, no patient with baseline eGFR >90 mL/min/1.73 m^2 shifted to 60−89 mL/min/1.73 m^2 at week 312.

Table 1. Changes of Renal Markers During the 2-Year GLOBE Study

Marker	Group	Baseline	Week 52	Week 104	LS mean (SE) change (%) from baseline to week 104	*P* value[a] (LdT vs LAM)
Serum creatinine, LS mean (SE), *μmol/L*	LdT (n = 680)	76 (9)	77 (9)	75 (9)	−5.0 (0.8)	<.0001
	LAM (n = 687)	76 (9)	80 (9)	80 (9)	+1.8 (0.8)	
Cockroft-Gault, LS mean (SE), *μmol/L*	LdT (n = 680)	112.0 (1.6)	111.1 (1.0)	111.7 (1.1)	+5.0 (1.0)	<.0001
	LAM (n = 687)	115.6 (1.6)	106.8 (1.0)	105.6 (1.1)	−1.1 (0.9)	
MDRD, LS mean (SE), *mL/min/1.73 m²*	LdT (n = 680)	103.2 (1.2)	104.1 (1.0)	105.7 (1.1)	+8.5 (1.1)	<.0001
	LAM (n = 687)	104.5 (1.1)	98.0 (0.95)	97.2 (1.02)	−0.5 (1.1)	
CKD-EPI, LS mean (SE), *mL/min/1.73 m²*	LdT (n = 680)	104.4 (0.9)	104.5 (0.7)	104.7 (0.6)	+4.8 (0.7)	<.0001
	LAM (n = 687)	105.1 (0.9)	100.4 (0.6)	99.7 (0.6)	−0.6 (0.7)	

LAM, lamivudine; LdT, telbivudine; LS, least square.
[a]*P* value, for testing treatment difference, was derived from analysis of covariance modeling, including treatment, country, and baseline value as covariates.

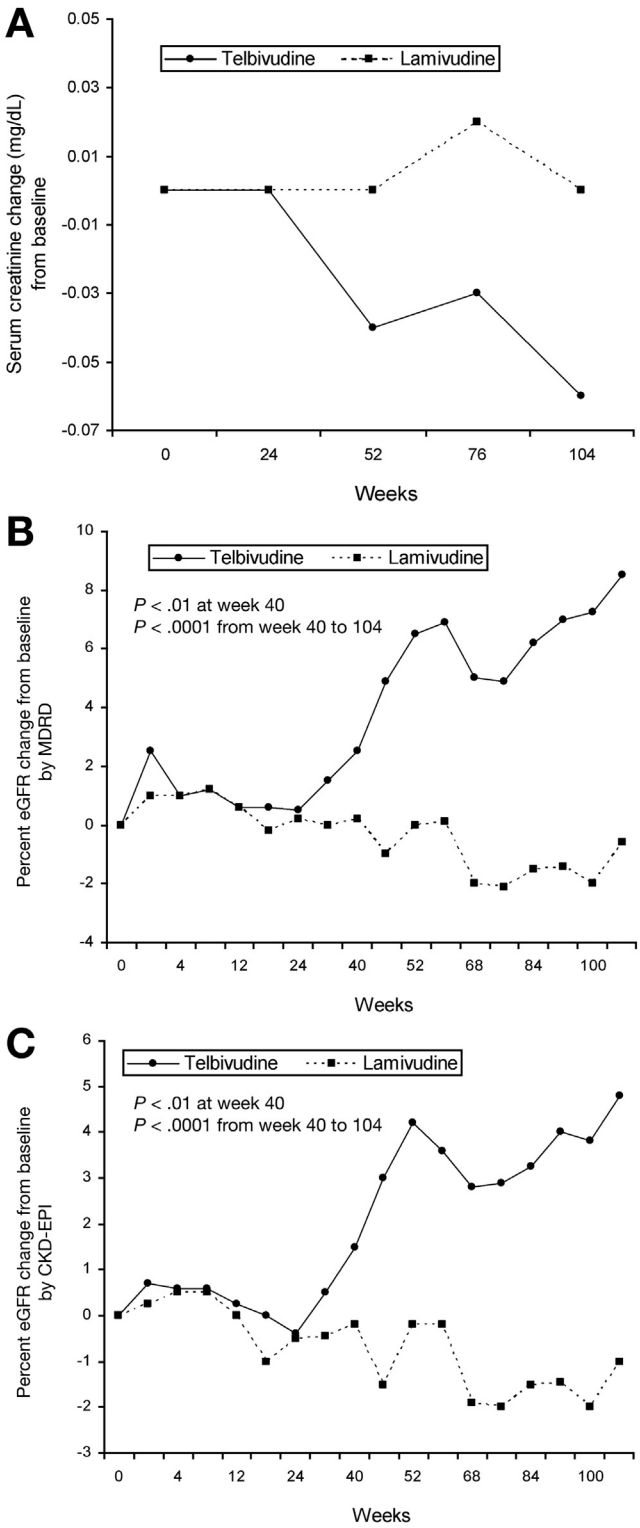

Figure 1. Evolution of renal function by treatment groups over 2 years as assessed by: (*A*) SCr; (*B*) eGFR, as calculated by the MDRD formula; (*C*) eGFR as calculated by CKD-EPI formula. Creatinine clearance (CKP-EPI or MDRD formula) was calculated at each time point with analysis of covariance modeling, including treatment, country, and baseline values as co-factors (last observation carried forward method for the intent-to-treat population of GLOBE study; n = 680 in telbivudine group and n = 687 in lamivudine group).

Maintenance of eGFR Improvement in Patients Off Treatment

Patients off treatment (telbivudine or lamivudine) at the end of studies GLOBE/015 were followed up during the 2-year extension study. At the end of GLOBE/015 studies, mean eGFR were 107.0 (n = 66) and 98.7 mL/min/1.73 m^2 (n = 57) in patients from telbivudine and lamivudine groups, respectively ($P = .037$). After 2 years off treatment, eGFR remained stable compared with extension study baseline: −0.9% in patients of telbivudine group and −1.2% in lamivudine group ($P = .8265$), respectively.

eGFR Improvement in Patients Switching From Lamivudine to Telbivudine

The effect of switch from lamivudine to telbivudine on renal function was analyzed in patients who received 2 years of lamivudine in GLOBE/015 studies and rolled over to extension study to receive telbivudine for 2 additional years. After 104 weeks of lamivudine treatment, eGFR change from baseline was +5.5 mL/min/1.73m^2 ($P < .0001$; n = 299), corresponding to +8.9%. At week 208 (2 years after switch to telbivudine), the change from baseline of extension study A2303 was +7.7 mL/min/1.73m^2 ($P < .0001$; n = 260), corresponding to +9.6%.

eGFR Changes in Special Populations of GLOBE Study (>50 Years, Insufficiency Stage and Advance Liver Fibrosis)

A subanalysis of patients with baseline CKD stage 2 (60−89 mL/min/1.73 m^2), demonstrated that 72.3% of patients receiving telbivudine, had eGFR improvement to ≥90 mL/min after 104 weeks of treatment in comparison to 52.6% of patients in the lamivudine-treated group (Table 3). In patients with baseline eGFR ≥90 mL/min, 91.2% (382 of 419) had stable eGFR, in comparison to 59.8% (266 of 445) of patients in the lamivudine-treated group. As shown in Figure 2, the eGFR increased in telbivudine-treated patients by 8.5% after 2 years. This improvement was even greater in those CHB subpopulations at greatest risk of renal dysfunction: patients with age older than 50 years (+11.4%) and patients with baseline CKD stage 2 (+17.2%). Lamivudine treatment was associated with decrease in eGFR or only modest increase.

Similar telbivudine-associated improvements in renal function were also observed in the subpopulation of GLOBE study with severe fibrosis or cirrhosis at baseline (Ishak fibrosis score [IF] ≥ 3). Mean changes of eGFR levels after 104 weeks of treatment with IF ≥ 3 were +6.1 mL/min/1.73 m^2 (8.0%, n = 182) in telbivudine group and −5.0 mL/min/1.73 m^2 (−4.6%; n = 255) in lamivudine group ($P < .0001$ for treatment groups comparisons); with IF ≥ 4, changes were +7.6 mL/min/1.73 m^2 (+10.4%, n = 66) in telbivudine group and −1.4 mL/min/1.73 m^2 (+0.1%, n = 80) in lamivudine group ($P = .0004$ for treatment groups comparison); with IF 5−6, changes were +5.2 mL/min/1.73 m^2 (+7.2%, n = 33) in telbivudine group and −0.6 mL/min/1.73 m^2 (+2.3%; n = 46) in

Table 2. Summary of eGFR (MDRD) Change Over Time in Telbivudine-Treated Patients (2-Year GLOBE Study and Extensions, Safety Population)

Treatment duration	n	Mean (SD)	Mean change eGFR from baseline, *mL/min/1.73 m²*	*P* value[a]	Patients with baseline eGFR 60−90 mL/min/1.73 m² shifted to >90 mL/min/1.73 m², % (n)
Feeder study baseline	655	94.9 (19.7)	NA	NA	NA
2 years	637	112.3 (23.0)	17.8 (24.8)	<.0001	72.3 (256)
3 years	587	115.4 (26.7)	21.0 (29.1)	<.0001	80.6 (268)
4 years	511	109.9 (24.4)	14.9 (28.1)	<.0001	74.0 (223)

NA, not applicable.
[a]Paired *t* test for comparison with feeder baseline.

lamivudine group ($P = .1018$ for treatment groups comparisons).

In patients with CKD stage 2 at baseline, 79.7% (55 of 69) with IF ≥ 3, 83.3% (20 of 24) with IF ≥ 4 and 75% (3 of 4) with IF 5−6 shifted to GFR >90 mL/min/1.73 m² under telbivudine treatment and only 37.2% (35 of 94) with IF ≥ 3, 43.7% (14 of 32) with IF ≥ 4, and 41.1% (7 of 17) with IF 5−6 under lamivudine treatment.

The improvements in eGFR observed in this subpopulation of patients with severe fibrosis or cirrhosis were not related with virological response (either HBV DNA reduction from baseline or nondetectability after 104 weeks).

eGFR Changes in CHB Patients With Decompensated Cirrhosis

In the A2301 study, patients with decompensated CHB were randomized 1:1 to 104 weeks treatment with telbivudine or lamivudine.[23] Although eGFR declined during lamivudine treatment (−4.6 mL/min/1.73 m² at week 104; −4.6%), eGFR steadily improved in telbivudine-treated patients (+2.0 mL mL/min/1.73 m²; +2.0%; $P = .0231$). Among patients with CKD stage 2 at baseline, eGFR improved to >90 mL/min/1.73 m² at week 104 in 40.7% (11 of 27) of telbivudine-treated patients compared with 31.4% (11 of 35) of lamivudine-treated patients.

Correlation of eGFR Improvement With Baseline Virological Characteristics and Efficacy Markers

Treatment-related changes in eGFR (MDRD) in patients of GLOBE study with CKD stage 2 (baseline GFR 60−89 mL/min/1.73 m²) were assessed according to virologic and serologic responses (undetectable HBV DNA at week 104,

Table 3. Changes of eGFR Category (MDRD)[a] in GLOBE 2-Year Study by Treatment Groups[b]

	Patients in eGFR categories at end of study(2 years), n			
	<60	60−90	>90	Total
Telbivudine group, n				
Patients in eGFR categories at baseline, n				
<60	0	4	1	5
60−90	0	71	185	256
>90	1	36	382	419
Total	1	111	568	680
Shift from 60–90 to >90, % (n)	72.3 (185/256)			
Shift from >90 to 60–90, % (n)	8.6 (36/419)			
Lamivudine group				
Patients in eGFR categories at baseline, n				
<60	2	4	2	8
60−90	5	106	123	234
>90	1	78	266	445
Total	8	188	491	687
Shift from 60–90 to >90, % (n)	52.6 (123/234)			
Shift from >90 to 60−90, % (n)	17.5 (78/445)			

[a]eGFR (MDRD) categories in mL/min/1.73 m².
[b]Differences between telbivudine and lamivudine groups were statistically significant for the proportion of patients switching from eGFR 60−90 mL/min/1.73 m² to >90 mL/min/1.73 m² at week 104 ($P < .0001$) and for the proportion of patients maintaining eGFR >90 mL/min/1.73 m² at week 104 ($P = .0001$).

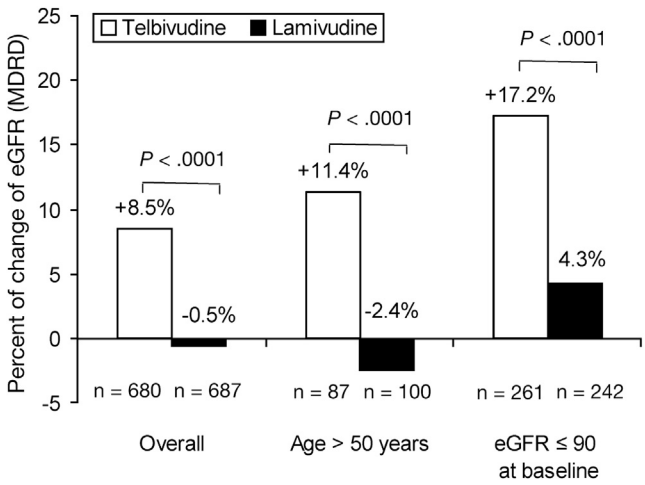

Figure 2. Effect of age and mild renal insufficiency (baseline eGFR at 60−90 mL/min/1.73 m^2) at baseline on eGFR (MDRD and CKD-EPI formulas) over 2 years in GLOBE study (intent-to-treat population, last observation carried forward). Data shown as percentages of least square (LS) mean changes of eGFR (mL/min/1.73 m^2). LS means and *P* values were obtained from analyses of covariance models, including treatment and country as factors for baseline; country and baseline GFR values were used as factors for post-baseline analysis.

resistance, baseline HBeAg status and HBeAg seroconversion at week 104). Changes in eGFR were similar in telbivudine-treated patients with or without complete virologic response (<300 copies/mL) at week 104: +17.2% (n = 157) and +20.3% (n = 99), respectively ($P = .28$) (least-square mean, MDRD). Patients with and without genotypic resistance, developed during first 2 years, had similar eGFR increase of +22.8% ± 3.7% (n = 59) vs +17.0% ± 2.8% (n = 197) ($P = .09$). Changes in eGFR were also similar in telbivudine-treated patients with and without viral suppression (HBV DNA > 5 $\log_{10}$ HBV DNA) and HBeAg-positive patients with and without complete response (HBV DNA undetectable, alanine aminotransferase normalization, and HBeAg seroconversion) (data not shown). No significant correlation was observed between eGFR improvement and HBV DNA decline ($P = .2771$ for telbivudine group and $P = .4435$ for lamivudine group).

Improvement in eGFR change was greater in HBeAg-positive patients than in HBeAg-negative patients: +8.3% vs +4.6% ($P = .0170$) at week 52 and +9.6% vs +6.5% ($P = .0607$) at week 104, respectively. However, HBeAg-positive patients were younger (mean age 32 years) than HBeAg-negative patients (mean age 43 years) at baseline in the GLOBE study. The influence of HBeAg status on eGFR improvement was investigated further in a multivariate analysis.

HBeAg seroconversion in HBeAg-positive patients was not associated with improvement in eGFR. In fact, in patients with CKD stage 2 at baseline, the improvement in eGFR after 104 weeks of telbivudine treatment was greater in those patients who failed to achieve HBeAg seroconversion (n = 114) than in those who did (n = 44): 7.3% vs 17.6% ($P = .022$).

Table 4. Independent Predictive Factors of eGRF Shift (MDRD) to >90 mL/min/1.73 m^2 at Year 2 in GLOBE Patients With eGFR at 60−90 mL/min/1.73 m^2 at Baseline

Predictive factors[a]	Comparator	Odd ratio[b]	95% Confidence interval	*P* values
Telbivudine	Lamivudine	2.509	1.663−3.784	<.0001
Age	NA[c]	0.940	0.923−0.958	<.0001
Caucasian	Asian	0.338	0.175−0.652	.0012
Other	Asian	0.429	0.183−1.005	.514

NA, not applicable.
[a]Other factors analyzed in multivariate analysis, but not found significant, were baseline alanine aminotransferase (<2 vs ≥2 × ULN), baseline HBV DNA (<9 vs ≥9 $\log_{10}$ copies/mL for HBeAg-positive and <7 vs ≥7 $\log_{10}$ copies/mL for HBeAg-negative patients), genotype (C vs non-C), HBeAg status (negative vs positive), and polymerase chain reaction status at week 24 (negative vs positive).
[b]Odds ratio calculated from logistic regression.
[c]Age was analyzed in multivariate analysis as continuous variable.

A multivariate analysis was performed on the GLOBE study patients, to assess which baseline factors could predict shifting from eGFR 60−90 mL/min/1.73 m^2 (MDRD) at baseline to ≥90 mL/min/1.73 m^2 at week 104 (Table 4). The independent predictors for improvement in eGFR were telbivudine treatment (telbivudine vs lamivudine, odds ratio = 2.509; $P < .0001$), younger age (odds ratio = 0.940; $P < .0001$) and non-Caucasian race (Caucasian vs non-Caucasian, odds ratio = .338; $P = .0012$). Baseline HBeAg status did not have an independent effect on eGFR change. The observed differences between HBeAg-positive and HBeAg-negative patients were most probably related to age differences at enrollment.

In patients with decompensated CHB (Study A2301), no significant correlation was evidenced between virological efficacy (HBV DNA < 4 $\log_{10}$ copies/mL or HBV DNA suppression) and improvement in eGFR.

Correlation of eGFR Improvement With Laboratory and Clinical Parameters

In an exploratory analysis, no correlation was reported between individual eGFR data from GLOBE study and laboratory parameters (eg, alanine aminotransferase, total bilirubin) and physiological parameters (eg, blood pressure, heart rate). In clinical studies, the incidence of CK elevations was increased in telbivudine-treated patients vs lamivudine-treated patients, although the clinical significance of this observation remains unclear. Therefore, the possible correlation between CK elevations and changes in renal function was determined in the subpopulation from the GLOBE study whose renal function shifted from eGFR 60−89 mL/min/1.73 m^2 at baseline to ≥90 mL/min/1.73 m^2 at 104 weeks. eGFR change was similar in patients with at least one documented elevation in CK level compared with those without (29.3% ± 3.6% vs

28.8% ± 6.2%; $P = .93$). Similarly, eGFR change was similar in patients with at least 2 documented elevated CK levels compared with those without (+23.6% ± 3.6% vs +18.4% ± 3.6%; $P = .072$).

Discussion

CKD is frequent in patients with chronic hepatitis B: 15%−30% have either baseline renal dysfunction or comorbidities associated with CKD, such as diabetes and hypertension.[5,6,13] GFR is an important indicator of kidney function, which allows detection, assessment, and management of chronic kidney diseases. Because GFR cannot be practically measured for routine purposes, calculations for GFR have been adopted based on SCr levels and other patient factors that determine renal function. The most widely used calculation is the Cockcroft-Gault equation, which relies on weight, age, sex, and SCr. Because the Cockcroft-Gault equation underestimates the degree of renal impairment in patients with advanced chronic liver disease, the MDRD calculation was developed to incorporate markers of nutritional status, namely serum albumin and urea levels. This formula has become the accepted method for estimating GFR in patients with chronic liver disease. The CKD-EPI calculation has recently been adopted to improve accuracy in patients with mild renal dysfunction.[24–26]

In the pivotal GLOBE study, a steady improvement in mean eGFR was observed in patients treated with telbivudine for 2 years, but not in those treated with lamivudine. The subsequent extension studies demonstrated that this improvement was maintained throughout 4−6 years of continuous telbivudine therapy. Of note, concordance was observed when GFR was estimated by each of the 3 eGFR calculations.

Treatment with telbivudine was associated with improvement in eGFR in patients older than 50 years of age and those with CKD stage 2 at baseline. One third of patients in the GLOBE study had CKD stage 2 at baseline. In this subpopulation at greatest risk for progressive renal dysfunction, eGFR improved to normal values (eGFR ≥90 mL/min/1.73 m^2) in 72.3% during 2 years of telbivudine therapy, a benefit that was maintained long term in the subsequent extension studies. It is intriguing whether this might provide similar benefit in patients with more severe renal dysfunction (eGFR <60 mL/min/1.73 m^2), including those with advanced fibrosis or cirrhosis, those with decompensated CHB, and those who have undergone liver transplantation.

In patients with advanced liver fibrosis (IF ≥ 3) or cirrhosis (IF 5−6) in the GLOBE study, eGFR significantly improved during telbivudine treatment. This improvement was not related to antiviral efficacy. CHB patients with cirrhosis have a high risk for renal impairment. A recent large randomized trial in patients with decompensated HBV-cirrhosis patients (Study A2301) reported that telbivudine therapy was also associated with a significant increase in eGFR compared with lamivudine after 2 years.[23]

After transplantation for CHB, oral antiviral therapy is administered long term to prevent HBV recurrence. This patient population has a high risk for CKD because of the concomitant use of calcineurin inhibitors and other nephrotoxic drugs, and because of the high prevalence of the comorbidities of diabetes and hypertension. Telbivudine appears to be safe and antiviral prophylaxis has been effective in this population.[27,28]

Telbivudine therapy has also been associated with improvement in renal function in other patient populations at high risk of renal impairment, including patients with acute-on-chronic liver failure, those receiving chemotherapy, and those with HBV-related nephritis.[27,29] Finally, it is of great interest to note that the combination of telbivudine with tenofovir, a potential nephrotoxic agent, was also associated with improvement in eGFR.[30–32]

The combined results from these studies containing >3500 patients with CHB suggest that long-term therapy with telbivudine leads to an improvement of renal function, in contrast to most other oral nucleo(t)sides against CHB.[33–36] The European Association for the Study of the Liver 2012 guidelines state that renal function decline has been reported with all nucleos(t)ides except perhaps for telbivudine, which seems to improve the creatinine clearance.[37] Adefovir and tenofovir might both be associated with nephrotoxicity, particularly in those patients with other risk factors for renal dysfunction, such as human immunodeficiency virus infection or liver transplantation. In a retrospective cohort analysis of CHB patients rescued with tenofovir for lamivudine resistance, the 5-year tenofovir treatment was associated with a significant decrease of eGFR (−10.3 mL/min/1.73 m^2 with MDRD equation; $P = .01$).[17] In a recent "real-life" study comparing patients receiving long-term therapy with either tenofovir or entecavir, SCr elevations (>18 μmol/L) were common in both treatment groups with confirmed increases of SCr significantly more frequent on entecavir treatment than tenofovir treatment (11% vs 2%; $P = .029$). Reduction in renal function (>20% decrease in eGFR) was common in both treatment arms (43% and 45%, respectively).[16]

The potential adverse impact of long-term antiviral therapy on renal function is an important issue in those CHB patients at particular risk for CKD, especially those older than 50 years of age and with baseline renal impairment. Therefore, the results from this review of telbivudine studies would support the recommendation from the 2012 European Association for the Study of the Liver guidelines, that baseline SCr levels and eGFR should be measured in all patients with CHB before commencing nucleos(t)ide therapy.[37] In addition, the baseline renal risk should be assessed for all patients at particular risk for CKD, including those with decompensated CHB, baseline moderate renal impairment (eGFR <60 mL/min), poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant nephrotoxic drugs, and those who have undergone solid organ transplantation. These guidelines also recommend appropriate on-treatment monitoring of eGFR and serum phosphate levels in all patients receiving nucleotide analogue therapy (adefovir or tenofovir) and monitoring of eGFR in

high-risk patients receiving nucleoside analogue therapy (ie, lamivudine, telbivudine, and entecavir).

The mechanism responsible for the improvement of renal function during long-term telbivudine therapy is still under investigation. A recent study compared telbivudine, entecavir, tenofovir, and adefovir on renal function and toxicity in normal rats.[38] Tenofovir showed renal histopathology changes (tubular-cell nuclear enlargement, intracellular accumulation of α-2 microglobulin) correlating with slight down-regulation of tubule-associated genes. Adefovir evidenced down-regulation of renal tubular-associated genes and autophagic vacuoles filled with mitochondria at different stages of degradation, which suggested involvement of mitochondrial toxicity.

The lack of improvement in eGFR within the first 24 weeks of telbivudine treatment during clinical studies would argue against interference by telbivudine on laboratory measurement of SCr or drug-induced glomerular hyperfiltration. The lack of association between change in eGFR and on-treatment virologic or serologic response would support a direct beneficial effect on the kidney rather than an indirect effect from HBV suppression. This hypothesis is further supported by lack of deterioration of renal function after virologic rebound due to emergence of telbivudine resistance. Even in patients who had achieved complete viral suppression (undetectable serum HBV DNA) on lamivudine therapy, switch to telbivudine resulted in improvement in eGFR. Finally, the improvement of eGFR during telbivudine therapy was maintained even after addition of a second, potentially nephrotoxic nucleos(t)ide. A possible effect of telbivudine could be on kidney structures or on inflammatory/fibrotic pathways. The mechanisms of nucleos(t)ide excretion in kidney should be also explored by studying the expression of transport pumps (eg, hOAT1, hOAT3, MRP4) in cells of proximal tubules.[39,40]

In conclusion, in global trials in compensated and decompensated patients, telbivudine therapy was associated with consistent increase in renal function (eGFR) across different patient populations. This effect was maintained during long-term therapy and was also observed in patients at greatest risk of renal dysfunction (older than 50 years of age or with baseline renal dysfunction). The mechanism of the beneficial effect of telbivudine therapy on renal function remains to be determined.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2013.09.031.

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Conflicts of interest
These authors disclose the following: Edward Gane is a current member of International Advisory Boards for Gilead Sciences and Novartis and is on the Speakers' Bureau for Gilead Sciences and Novartis. Gilbert Deray is an invited speaker for Gilead and Novartis. Yun-Fan Liaw is a member of International Advisory Boards for Roche, BMS, Novartis, and Gilead Sciences. Seng Gee Lim is on the Speaker's Bureau for GlaxoSmithKline Pharmaceuticals, Schering Plough Pharmaceuticals, and Bristol Myers Squibb Pharmaceuticals and Advisory Board member for Novartis, Bristol Myers Squibb, Idenix Pharmaceuticals, and Pfizer Pharmaceuticals. Ching-Lung Lai is an invited speaker for BMS. Adrian Di Bisceglie served as a speaker, a consultant, or an advisory board member for Roche (now Genentech), Vertex, Bristol-Myers Squibb, Merck, Anadys, Bayer, GlobeImmune, Pharmasset, Salix, and Tibotec; and has received research funding from Roche (now Genentech), Gilead, Idenix, Vertex, Bristol-Myers Squibb, Abbott, Anadys, Globe-Immune, Pharmaset, Transgene, and Tibotec. Didier Samuel is a consultant for Astellas, BMS, Gilead, Janssen-Cilag, LFB, MSD, Novartis, Roche, and Biotest. Alkaz Uddin: employee of Novartis Pharmaceuticals. Sophie Bosset is an employee of Novartis Pharma AG. Aldo Trylesinski is an employee of Novartis Pharma AG. The remaining authors disclose no conflicts.

Supplementary Material

The Supplementary Tables describe secondary analyses according to the 3 eGFR methods (MDRD, Cockcroft-Gault, CKD-EPI). The 3 methods lead to the same conclusions:

- Long-term extension study with telbivudine (Study A2303): Supplementary Table 1
- Off-treatment patients (A2303 Study): Supplementary Table 2
- Switch from lamivudine to telbivudine (Study A2303): Supplementary Table 3
- Special populations from GLOBE studies:

  Patients 50 years and older: Supplementary Table 4

  Renal insufficiency: Supplementary Table 5

  Severe fibrosis or cirrhosis: Supplementary Table 6
- Decompensated cirrhosis (Study A2301): Supplementary Table 7

Supplementary Table 1. Summary of eGFR Change Over Time in Telbivudine-Treated Patients (2-Year GLOBE Study and Extensions, Safety Population)

	n	Mean ± SD	Mean change ± SD of eGFR from baseline	*P* value[a]
MDRD, *mL/min/1.73 m²*				
Feeder study baseline	655	94.9 ± 19.7	NA	NA
2 years	637	112.3 ± 23.0	+17.8 ± 24.8	<.0001
3 years	587	115.4 ± 26.7	+21.0 ± 29.1	<.0001
4 years	511	109.9 ± 24.4	+14.9 ± 28.1	<.0001
Cockcroft-Gault, *mL/min*				
Feeder study baseline	640	101.9 ± 26.2	NA	NA
2 years	637	117.1 ± 27.1	+15.3 ± 22.9	<.0001
3 years	587	118.7 ± 28.4	+17.3 ± 25.4	<.0001
4 years	511	113.7 ± 27.7	+11.8 ± 25.3	<.0001
CKD-EPI, *mL/min/1.73 m²*				
Feeder study baseline	655	98.3 ± 16.6	NA	NA
2 years	637	110.7 ± 14.5	+12.8 ± 17.1	<.0001
3 years	587	111.3 ± 15.7	+13.4 ± 18.5	<.0001
4 years	511	107.9 ± 16.3	+9.5 ± 19.2	<.0001

NA, not applicable.
[a]Paired *t* test for comparison with feeder baseline.

Supplementary Table 2. Summary of eGFR Change in Patients Who Received 2 Years of Lamivudine in GLOBE/015 Studies and Rolled Over to Extension Study A2303 Off Treatment (Study A2303)

	Telbivudine			Lamivudine			*P* value for treatment group comparison[b]
	n	LS mean ± SE	LS mean ± SE change from baseline [% of change] (*P* value)[a]	n	LS mean ± SE	LS mean ± SE change from baseline [% of change] (*P* value)[b]	
MDRD, *mL/min/1.73 m²*							
Baseline Study A2303	66	107.0 ± 3.6	NA	57	98.7 ± 3.7	NA	.0370
Week 104	66	103.9 ± 2.4	−4.4 ± 2.4 [−0.9] (.0032)	57	103.3 ± 2.6	−5.0 ± 2.6 [−1.2] (.0296)	.8265
Cockcroft-Gault, *mL/min*							
Baseline Study A2303	66	107.9 ± 4.1	NA	57	103.0 ± 4.3	NA	.2812
Week 104	66	105.7 ± 2.9	−1.8 ± 2.9 [+0.6] (.0833)	57	105.9 ± 3.1	−1.6 ± 3.1 [+1.5] (.0987)	.9586
CKD-EPI, *mL/min/1.73 m²*							
Baseline Study A2303	66	105.7 ± 2.4	NA	57	100.5 ± 2.5	NA	.0498
Week 104	66	106.0 ± 1.8	−2.4 ± 1.8 [−1.2] (.0056)	57	105.5 ± 1.9	−2.9 ± 1.9 [−1.6] (.0300)	.7895

NOTE. Intent-to-treat population, last observation carried forward method.
LS, least square; NA, not applicable.
[a]Paired *t* test for comparison with feeder baseline within treatment group.
[b]For baseline values, analysis of covariance (ANCOVA) modeling included treatment and country as covariates; for post-baseline values, ANCOVA modeling included treatment, country, and baseline values as covariates.

Supplementary Table 3. Summary of eGFR Change in Patients Who Received 2 Years of Lamivudine in GLOBE/015 Studies and Rolled Over to Extension Study A2303 to Receive Telbivudine for 2 Additional Years

	Lamivudine treatment during GLOBE/015 studies (2 y)				Telbivudine treatment during A2303 Study (2 y)			
	n	eGFR at baseline, mean ± SD	Change from baseline, mean ± SD [% of change]	*P* value[a]	n	eGFR at baseline, mean ± SD	Change from baseline, mean ± SD [% of change]	*P* value[a]
MDRD, *mL/min/1.73 m²*	299	93.9 ± 22.0	+5.5 ± 22.3 [+8.9]	<.0001	299	99.4 ± 19.3	+7.7 ± 19.2 [+9.6]	<.0001
Cockcroft-Gault, *mL/min*	299	100.7 ± 27.1	+6.1 ± 20.9 [+8.5]	<.0001	299	106.9 ± 26.5	+5.1 ± 16.7 [+6.2]	<.0001
CKD-EPI, *mL/min/1.73 m²*	299	96.8 ± 16.9	+5.7 ± 17.3 [+7.8]	<.0001	299	102.4 ± 16.4	+4.4 ± 13.2 [+5.8]	<.0001

[a]Paired *t* test for comparison with baseline.

Supplementary Table 4. eGFR Change in Patients Older Than 50 Years From GLOBE Study

	Telbivudine			Lamivudine			
	n	LS mean ± SE	LS mean ± SE change from baseline (*P* value)[a] [% of change]	n	LS mean ± SE	LS mean ± SE change from baseline (*P* value)[a] [% of change]	*P* value for treatment group comparison[b]
MDRD, *mL/min/1.73 m²*							
Baseline GLOBE Study	87	91.4 ± 2.3	NA	100	91.3 ± 2.2	NA	.9654
Week 104	87	98.8 ± 1.8	+8.4 ± 1.8 [+11.4] (.0001)	100	87.0 ± 1.7	−3.4 ± 1.7 [−2.4] (.0513)	<.0001
Cockcroft-Gault, *mL/min*							
Baseline GLOBE Study	87	97.3 ± 2.9	NA	100	94.0 ± 2.8	NA	.3638
Week 104	87	97.2 ± 1.8	+5.0 ± 1.7 [+6.4] (.0264)	100	87.9 ± 1.7	−4.3 ± 1.7 [−3.4] (.0074)	<.0001
CKD-EPI, *mL/min/1.73 m²*							
Baseline GLOBE Study	87	89.2 ± 1.6	NA	100	88.6 ± 1.6	NA	.7520
Week 104	87	92.6 ± 1.2	+4.3 ± 1.2 [+6.4] (.0006)	100	84.9 ± 1.1	−3.4 ± 1.1 [−3.0] (.0466)	<.0001

NOTE. Intent-to-treat population, last observation carried forward method.
LS, least square; NA, not applicable.
[a]Paired *t* test for comparison with baseline within treatment group.
[b]For baseline values, analysis of covariance (ANCOVA) modeling included treatment and country as covariates; for post-baseline values, ANCOVA modeling included treatment, country, and baseline values as covariates.

Supplementary Table 5. eGFR Change in Patients From GLOBE Study With Renal Insufficiency (eGFR $\leq$ 90 mL/min/1.73 m^2)

	Telbivudine			Lamivudine			*P* value for treatment group comparison[b]
	n	LS mean ± SE	LS mean ± SE change from baseline [% of change] (*P* value)[a]	n	LS mean ± SE	LS mean ± SE change from baseline [% of change] (*P* value)[a]	
MDRD, *mL/min/1.73 m²*							
Baseline GLOBE Study	261	79.9 ± 0.85	NA	242	80.0 ± 0.8	NA	.9308
Week 104	261	92.1 ± 1.6	+13.1 ± 1.6 [+17.2] (< .0001)	242	81.9 ± 1.5	+2.9 ± 1.5 [+4.3] (< .0001)	<.0001
Cockcroft-Gault, *mL/min*							
Baseline GLOBE Study	210	79.2 ± 1.1	NA	195	78.3 ± 1.1	NA	.2746
Week 104	210	86.9 ± 1.6	+9.0 ± 1.6 [+11.7] (< .0001)	195	79.9 ± 1.6	+2.1 ± 1.6 [+2.6] (< .0001)	<.0001
CKD-EPI, *mL/min/1.73 m²*							
Baseline GLOBE Study	188	80.7 ± 1.0	NA	160	79.2 ± 1.0	NA	.0764
Week 104	188	90.7 ± 1.4	+11.5 ± 1.4 [+15.1] (< .0001)	160	81.8 ± 1.5	+2.6 ± 1.5 [+3.7] (< .0001)	<.0001

NOTE. Intent-to-treat population, last observation carried forward method.
LS, least square; NA, not applicable.
[a]Paired *t* test for comparison with baseline within treatment group.
[b]For baseline values, analysis of covariance (ANCOVA) modeling included treatment and country as covariates; for post-baseline values, ANCOVA modeling included treatment, country, and baseline values as covariates.

Supplementary Table 6. eGFR Change in Patients From GLOBE Study According to Ishak Fibrosis Score (Week 104)

	Telbivudine			Lamivudine			*P* value for treatment group comparison of eGFR change[b]
	n	LS mean ± SE eGFR at baseline	LS mean ± SE change of eGFR at week 104 from baseline [% of change] (*P* value)[a]	n	LS mean ± SE eGFR at baseline	LS mean ± SE change of eGFR at week 104 from baseline [% of change] (*P* value)[a]	
MDRD, *mL/min/1.73 m²*							
IF ≥ 3	182	98.3 ± 2.0	+6.1 ± 1.6 [+8.0] (<.0001)	225	98.4 ± 1.9	− 5.0 ± 1.6 [−4.6] (.5208)	<.0001
IF ≥ 4	66	99.3 ± 3.0	+7.6 ± 2.1 [+10.4] (.0003)	80	100.3 ± 3.0	− 1.4 ± 2.1 [+0.1] (.1315)	.0004
IF ≥ 5	33	102.8 ± 4.4	+5.2 ± 2.7 [+7.2] (.0449)	46	99.6 ± 4.4	− 0.6 ± 2.7 [+2.3] (.1283)	.1018
IF ≥ 6	16	107.6 ± 5.7	+2.8 ± 3.6 [+3.5] (.3526)	21	102.5 ± 5.7	− 8.8 ± 3.4 [−6.3] (.9014)	.0710
Cockcroft-Gault, *mL/min*							
IF ≥ 3	182	109.5 ± 2.7	+4.4 ± 1.8 [+5.1] (.0001)	225	110.6 ± 2.7	− 5.0 ± 1.8 [−3.9] (.8897)	<.0001
IF ≥ 4	66	110.1 ± 4.1	+5.8 ± 2.4 [+6.8] (.0015)	80	113.8 ± 4.1	− 2.4 ± 2.5 [−1.2] (.3200)	.0050
IF ≥ 5	33	110.6 ± 5.9	+1.3 ± 3.0 [+2.4] (.1336)	46	120.1 ± 5.8	− 2.5 ± 3.1 [−0.0] (.3087)	.3351
IF ≥ 6	16	116.7 ± 7.2	− 2.2 ± 4.3 [−0.2] (.9387)	21	126.7 ± 7.1	− 6.1 ± 4.6 [−6.3] (.8749)	.5499
CKD-EPI, *mL/min/1.73 m²*							
IF ≥ 3	182	98.7 ± 1.6	+2.4 ± 1.1 [+3.5] (<.0001)	225	98.8 ± 1.6	− 4.9 ± 1.1 [−4.8] (.3663)	<.0001
IF ≥ 4	66	98.2 ± 2.4	5.0 ± 1.4 [+7.1] (<.0001)	80	98.5 ± 2.4	− 1.6 ± 1.4 [−0.6] (.0224)	.0001
IF ≥ 5	33	100.1 ± 3.4	+3.3 ± 1.9 [+5.5] (.0143)	46	97.1 ± 3.4	+0.9 ± 1.9 [3.1] (.0336)	.3112
IF ≥ 6	16	103.6 ± 4.3	+0.0 ± 1.8 [+1.7] (.1597)	21	97.7 ± 4.2	− 3.3 ± 1.7 [−2.2] (.2922)	.2273

NOTE. Intent-to-treat population, last observation carried forward method.
LS, least square.
[a]Paired *t* test for comparison with baseline within treatment group.
[b]For baseline values, analysis of covariance (ANCOVA) modeling included treatment and country as covariates; for post baseline values, ANCOVA modeling included treatment, country, and baseline values as covariates.

Supplementary Table 7. eGFR Change in Patients From Study A2301 in Patients With Decompensated Cirrhosis

	Telbivudine			Lamivudine			
	n	LS mean ± SE	LS mean ± SE change from baseline	n	LS mean ± SE	LS mean ± SE change from baseline	*P* value for treatment group comparison[a]
MDRD, *mL/min/1.73 m²*							
Baseline Study A2301	114	102.1 ± 3.1	NA	114	99.7 ± 2.9	NA	.4539
Week 104	114	104.9 ± 2.7	+2.0 ± 2.7	114	98.3 ± 2.6	−4.6 ± 2.6	.0231
Cockcroft-Gault, *mL/min*							
Baseline Study A2301	114	120. 0 ± 4.3	NA	114	114.1 ± 4.0	NA	.1952
Week 104	114	105.0 ± 2.9	0.0 ± 2.9	114	100.9 ± 2.7	−4.2 ± 2.7	.1754
CKD-EPI, *mL/min/1.73 m²*							
Baseline Study A2301	114	98.4 ± 2.0	NA	114	95.9 ± 1.9	NA	.2622
Week 104	114	97.5 ± 1.7	−0.7 ± 1.7	114	94.6 ± 1.7	−3.6 ± 1.7	.1255

NOTE. Intent-to-treat population, last observation carried forward method.
LS, least square; NA, not applicable.
[a]For baseline values, analysis of covariance (ANCOVA) modeling included treatment and country as covariates; for post baseline values, ANCOVA modeling included treatment, country and baseline values as covariates.